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EVIDENCE-BASED REVIEW

Prevention of bacterial meningitis: An overview of Cochrane systematic reviews ☆

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Summary
Acute bacterial meningitis (ABM) is an acute inflammation of leptomeninges caused by bacteria, and has a case fatality rate of 10–30%. Prevention strategies, such as vaccination and prophylactic antibiotics, can prevent ABM and have substantial public health impact by reducing the disease burden associated with it. The aim of this paper is to summarize the main findings from Cochrane systematic reviews that have considered the evidence for measures to prevent ABM. We assessed the evidence available in the Cochrane Library. We found five Cochrane reviews focused on the prevention of ABM; three with use of vaccination and two with prophylactic antibiotics. Polysaccharide serogroup A vaccine is strongly protective for the first year, against serogroup A meningococcal meningitis in adults and children over 5 years of age. Meningococcal serogroup C conjugate (MCC) vaccine is safe and effective in infants. *Haemophilus influenzae* type b (Hib) vaccine is safe and effective against Hib-invasive disease at all ages. Ceftriaxone, rifampicin and ciprofloxacin are the most effective prophylactic antibiotics against *Neisseria meningitidis*. There is sufficient evidence to use polysaccharide serogroup A vaccine to prevent serogroup A meningococcal meningitis, MCC conjugate vaccines to prevent meningococcal C meningitis and Hib conjugate vaccine to prevent Hib infections. More studies are needed to evaluate the effects of Hib conjugate vaccine on mortality. Further, studies are required to compare the relative effectiveness of ceftriaxone, ciprofloxacin and rifampicin in chemoprophylaxis against meningococcal infection.

☆The following Cochrane reviews have been cited in this evidence-based review. Patel M., Lee C.K. Polysaccharide vaccines for preventing serogroup A meningococcal meningitis, Issue 1, 2005; Conterno LO, et al. Conjugate vaccines for preventing meningococcal C meningitis and septicaemia, Issue 3, 2006; Swingler G, et al. Conjugate vaccines for preventing *Haemophilus influenzae* type B infections, Issue 4, 2003; Fraser A, et al. Antibiotics for preventing meningococcal infections, Issue 1, 2005; Ratilal B, et al. Antibiotic prophylaxis for preventing meningitis in patients with basilar skull fractures, Issue 1, 2006.

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Background

Acute bacterial meningitis (ABM) is defined as an acute inflammation of leptomeniges (pia-arachnoid) caused by bacteria. ABM is a major cause of death and disability, especially in developing countries. Despite advances in neuroimaging and critical care, the case fatality rate of ABM remains around 10–30%. An additional 5–40% of cases have only partial recovery with late sequelae.[1] Effective preventive and treatment strategies are required to reduce mortality and morbidity.

In this paper, we review the available evidence on measures for preventing ABM. We will restrict ourselves to interventions that have been the subject of Cochrane systematic reviews, as these reviews make systematic attempts to synthesize high-quality evidence from randomized-controlled trials (RCTs), and may be considered the highest level in the hierarchy of evidence.

Methods

In October 2006, we searched the Cochrane Library (Issue 3, 2006) for relevant reviews using 'meningitis' as a search term. The titles of all the search results were examined to select reviews on prevention of ABM. The full text of each of the selected reviews were printed out and studied.

Results

The initial search yielded 127 hits. After examining the titles, we selected five reviews as relevant to the topic. Reviews were excluded if they addressed other types of meningitis (e.g. tubercular or cryptococcal), or if they did not address interventions for ABM but were found by the search strategy because the word 'meningitis' was mentioned for other reasons.

Although some reviews included both RCTs and non-randomized studies, we have considered mainly the results of only the RCTs. Several Cochrane reviews have addressed the efficacy of vaccines to prevent pneumococcal infection, including invasive infection. However, none of these reviews contain information that specifies the effect of vaccines on the incidence of pneumococcal meningitis. This applies to reviews on vaccines to prevent pneumococcal infection. Protocols were also excluded. A brief summary of all the reviews is presented in Table 1. For each selected review, we provide below the details of methods and results.

Methods common to all reviews

All the included Cochrane reviews were selected after searching the literature in various databases, mainly Medline, Embase and the Cochrane Central Register of Controlled Trials. In addition, most reviewers used other strategies to find relevant studies. The strategies included searching of specialized databases within the Cochrane Collaboration, such as the Cochrane Airways Group Trials Register or Cochrane Infectious Diseases Group Trial Register, checking references of relevant articles, writing to manufacturers of vaccines and drugs, and writing to authors for additional studies.

More than one reviewer independently assessed eligibility of the studies for their review, their methodological quality and extracted the data. All reviews used the Cochrane Collaboration software Revman to synthesize their results.

Cochrane review on polysaccharide vaccines for serogroup A meningococcal meningitis

Serogroups A–C of *Neisseria meningitidis* account for most cases of meningococcal meningitis throughout the world. Although serogroup A dominates across Africa, serogroups B and C are responsible for most cases in industrialized countries.[7,8] Large epidemics of serogroup A occur in the sub-Saharan 'meningitis belt' that extends from Ethiopia in the east to Senegal in the west.[9,10]

The main objectives of this review were to determine the effect of polysaccharide serogroup A vaccine for preventing serogroup A meningococcal meningitis, to assess age-specific effects of this vaccine, the effects of booster doses in children under 5 years of age and the duration of protection in children and adults.

The last search of the literature for this Cochrane review was carried out in November 2004. The authors included eight RCTs; they also included one case–control study and one historical cohort study, but both had high risk of bias and low statistical power. The unit of allocation was individual participant in three trials, community clusters in four, school class in one, household in one and village in one.

The eight RCTs revealed consistent results. The remarkable consistency across the trials conducted in widely diverse settings, with epidemic and endemic disease, in developed and developing countries provided support for generalizability of research findings.

Overall, the vaccine efficacy in the eight trials combined was 95% (95% confidence interval [CI] 87–99%) in the first year after vaccination, in participants aged over 5 years. There was insufficient evidence to determine the duration of protection beyond 1 year after vaccinating adults and children over 5 years of age. In one study from Finland, the vaccine was protective in children aged 3 months to 5 years. However, the vaccine efficacy within the age sub-categories of these children could not be determined because of the small number of children in the study. For the same reason, the effect of single versus two doses of vaccine in children aged 3–17 months of age could not be determined.

The authors of this review concluded that the polysaccharide serogroup A vaccine is strongly protective against serogroup A meningococcal meningitis in adults and children over 5 years of age for the first year after vaccination. The vaccine is probably also protective in children aged 3 months to 5 years, but only a few trials have addressed this issue. There is insufficient evidence to determine protection beyond 1 year after vaccination and to support or refute the use of booster doses in children younger than 2 years of age.

Cochrane review on conjugate vaccines for preventing meningococcal C meningitis and septicaemia

Serogroup C meningococcal meningitis has been recorded in epidemics in Africa, the Middle East and the Indian

Table 1 Summary of Cochrane reviews.

Topic	Most recent search	Number of studies included	Conclusions
Polysaccharide vaccines for preventing serogroup A meningococcal meningitis[2]	2004	8 RCT, 2 non-RCTs	The polysaccharide serogroup A vaccine is strongly protective against serogroup meningococcal meningitis in children over 5 years of age and adults for the first year after vaccination. Insufficient evidence to determine efficacy and duration of protection across age strata in children younger than 5 years of age. Insufficient evidence to determine value of booster dose in children younger than 2 years of age.
Conjugate vaccines for preventing meningococcal C meningitis and septicaemia[3]	2005	14 RCTs, 8 CCTs	MCC vaccine is clinically effective. MCC vaccine is more immunogenic than MPLS vaccine in all age groups. MCC vaccine seems to be safe and able to induce immunological memory in all age groups. MCC is preferred as a booster dose for those previously vaccinated with MPLS.
Conjugate vaccines for preventing *Haemophilus influenzae* type b infections[4]	2003	5 RCTs	Hib vaccine is safe and effective against Hib disease, size of effect is uncertain. In resource-poor settings, use of vaccine will depend on cost, local burden of Hib disease and competing priorities. Effects of Hib conjugate vaccine on either Hib-specific or on all-cause mortality were uncertain.
Antibiotics for preventing meningococcal infections[5]	2004	24 RCTs	Despite rifampicin's eradication, efficacy of its use in an outbreak setting might lead to circulation of isolates resistant to rifampicin, so use of ciprofloxacin and ceftriaxone should be considered. Prophylactic treatment has proven to reduce risk of disease among household contacts, thus placebo-controlled trials are unethical.
Antibiotic prophylaxis for preventing meningitis in patients with basilar skull fractures[6]	2005	5 RCTs, 17 non-RCTs	No effect of prophylactic antibiotics on the prevention of meningitis in patients with BSF, regardless of CSF leakage.

CCT, controlled clinical trial; CSF, cerebrospinal fluid; Hib, *Haemophilus influenzae* type B; MCC, meningococcal serogroup; MPLS, meningococcal polysaccharide.

sub-continent. It has been responsible for 25–68% of all meningococcal cases in Europe, America and Australia.[11] Age-specific incidence peaks between 6 and 12 months after birth in developed countries.[12] Vaccines against serogroup C meningococcal disease are available in combination with serogroups A, W-135 and Y, based on their capsular polysaccharides. However, the polysaccharide vaccines have several limitations. The serogroup C component is not immunogenic in infants under 2 years of age,[13–16] thus failing to protect those at greatest risk of disease. In older children, there is protection but it is short lived. These deficiencies of the polysaccharide vaccines have been overcome with the development of conjugate vaccines, in which the capsular polysaccharides are covalently linked to carrier proteins. Tetanus toxoid, diphtheria toxoid or CRM_{197}, a non-toxic mutant of diphtheria toxin, have been used as carrier proteins. Conjugation converts the thymus-independent polysaccharide into a thymus-dependent immunogen. This results in engagement of T cells in the induction of antibodies in infants and memory responses. The main objective of this review was to assess the immunogenecity, safety and efficacy of the conjugate vaccines in prevention of serogroup C meningococcal meningitis.

The last search of the literature for this review was carried out in September 2005. The authors set out to identify RCTs and controlled clinical trials (CCTs). However, RCTs evaluated only immunogenicity and safety. In the absence of any RCT with clinical end points, the authors decided to include population-based observational studies to determine clinical efficacy of the vaccines. All age groups from infants to adults were included.

Twenty-four studies involving 28 reports were included. Eighteen were RCTs and four observational studies. Overall, the quality of RCTs was good. The conjugated vaccine meningococcal serogroup C conjugate (MCC) was directed against serogroup C (11 studies), AC (5 studies) or ACYW135 (1 study). One study evaluated a combination 9–valent pneumococcal MCC. The oligosaccharide C was conjugated to CRM_{197} (cross-reacting material) non-toxic mutant of diphtheria toxin in all except three trials. In these three trials, the oligosaccharide was conjugated to tetanus toxoid.

The RCTs showed that MCC vaccine was highly immunogenic in infants after two and three doses, in toddlers after one and two doses and after a single dose in older age groups.

The authors of the review concluded that, after one dose, the MCC vaccine was shown to be safe in infants. The adverse events reported (more frequently in infants) were as follows: fever (1–5%), irritability (38–67%), crying more than expected (1–13%), redness (6–97%), tenderness (11–13%) and swelling (6–42%) at the site of vaccination.

Observational studies showed that there was a rapid decline in group C meningococcal disease in England, Quebec and Spain, following the introduction of MCC vaccination into the routine infant schedule, together with an extensive catch-up vaccination campaign of young children and teenagers. The studies screened the population for meningococcal C disease and evaluated the effectiveness of the vaccine using the screening method explained below.

The screening method of analysis is based on a comparison of the proportion vaccinated among the cases and the population.[17,18] On the basis of this method of analysis, after 1 year, MCC vaccine effectiveness was established to be 83–99.5% in those vaccinated after 7 months of age. In general, conjugate vaccines generated higher titers than polysaccharide vaccines. Immune responses seem to be better when the vaccine is given later in the first year of life. Most studies used three doses in infants but two doses may be adequate, particularly with the tetanus toxoid conjugate. In children aged between 12 and 18 months of age, two doses of MCC generates high antibody titers and most have protective titers after single dose, particularly with the tetanus toxoid conjugate. One dose seems to be sufficient after 2 years of age. According to the observational studies, there can be a decline in protection after primary vaccination, and this may be more marked when children are vaccinated in the first year of life. The MCC vaccine is found to be more immunogenic than meningococcal polysaccharide (MPLS) in all age groups, and is preferred as a booster dose for those previously vaccinated with MPLS.

The authors supported the inclusion of MCC vaccine into national immunization programs in areas where meningococcal C disease is a substantial public health problem.

Cochrane review on conjugate vaccines for preventing *Haemophilus influenzae* type b infections

H. influenzae type b (Hib) is one of the 'big three' causes of ABM and pneumonia in children under 5 years of age. It is estimated to cause at least 3 million cases of serious disease and hundreds of thousands of deaths annually, worldwide (WHO, 1998). The main objective of this review was to determine the effects of conjugate Hib vaccine in preventing Hib disease or death in children under 5 years and to determine whether Hib conjugate vaccine causes any serious adverse effects. The last search of the literature for the Cochrane review was conducted in April 2003. The authors included four RCTs and one quasi-randomized trial. The overall quality of the randomized trials was good. The study population consisted of children younger than 5 years of age, irrespective of HIV status. Outcomes planned to be studied were all-invasive Hib diseases, all-cause mortality, Hib-specific mortality, cause-specific mortality from meningitis and pneumonia, and any adverse events due to Hib vaccination.

The use of vaccine was associated with risk reduction of 80% (RR 0.20, 95% CI 0.07–0.54). The size of effect did not seem to differ with different vaccine types, number of vaccine doses or age at first vaccination.

Hib-related mortality data were available from two trials included in the meta-analysis, and showed a non-significant trend towards benefit, with an estimate of about 70% reduction (relative risk: 0.29), but the wide confidence interval (0.07–1.20) did not exclude a harmful effect, and also reflected the paucity of information available. There were no reports of any serious adverse effects from any of these trials involving 257,000 infants.

The authors of the review concluded that Hib vaccine is safe and effective against Hib-invasive disease; however, the size of effect was uncertain. Effects of Hib conjugate vaccine on either Hib-specific or on all-cause mortality were uncertain. It was concluded that, in resource-poor settings, use of vaccine will depend on its cost, local burden of Hib disease and competing priorities.

Cochrane review on antibiotics for preventing meningococcal infections

Meningococcal meningitis is spread by person-to-person contact through respiratory droplets. The causative organism, *N. meningitis*, first colonizes the nasopharynx of contacts, turning them into carriers, who spread the disease to others, but also some of them develop meningitis or septicaemia. Individuals in close contact with people with meningococcal disease are at increased risk for developing disease (WHO, 2003a).[19] Antibiotic prophylaxis is considered for those in close contact with cases (e.g., people living in the same household during the first 7 days after a case) and in populations with known high carriage rates.

The authors set out to summarize the evidence of effectiveness of different antibiotic prophylactic treatments in (1) preventing secondary cases of meningococcal disease after contact with a person with meningococcal disease, both within and outside the household; (2) preventing cases of meningococcal disease in populations with a high rate of *N. meningitidis* carriers; and (3) eradicating *N. meningitidis* from the pharynx in healthy carriers of *N. meningitidis*.

Authors included randomized or quasi-randomized clinical trials in *N. meningitdis* carriers and healthy individuals exposed to people with meningococcal disease or belonging to a population with a high rate of *N. meningitidis* carriers, regardless of their carrier status. Outcomes studied were mortality and morbidity due to meningococcal disease and failure to eradicate *N. meningitidis* from the nasopharynx.

The last search of the literature for the Cochrane review was conducted in September 2004. The authors included 23 randomized and two quasi-randomized trials. Study population included household contacts (six trials), army recruits (seven trials), students (four trials), volunteers (three), children (one) and unspecified (one). There were no deaths

related to meningococcal disease (three unrelated deaths were recorded in one study). Two had one case each of meningococcal disease but one occurred before prophylaxis had begun and the second occurred 12 weeks after treatment with rifampicin. Three other trials did not have any meningococcal disease. Clinical effectiveness (prevention of disease) of chemoprophylaxis, therefore, could not be assessed. All trials reported failure to eradicate *N. meningitidis* from the nasopharynx as the main outcome.

At 1 week after treatment, effective antibiotics (compared with placebo) were ciprofloxacin (relative risk [RR] 0.04; 95% CI 0.01–0.12), rifampicin (RR 0.17; 95% CI 0.12–0.24), minocycline (RR 0.30; 95% CI 0.19–0.45) and ampicillin (RR 0.41; 95% CI 0.25–0.66). Between 1 and 2 weeks' follow-up, only rifampicin (RR 0.20; 95% CI 0.14–0.29) and ciprofloxacin (RR 0.03; 95% CI 0.00–0.42) proved effective.

Minocycline and penicillin were found effective, although 95% CIs were wide. Ceftriaxone was more effective than rifampicin (only one study RR 5–93; 95% CI 1.22–28.68). Rifampicin continued to be effective compared with placebo up to 4 weeks after treatment, but resistant isolates were seen after prophylaxis.

Authors of the review concluded that the most effective antibiotics to achieve eradication of *N. meningitidis* from nasopharynx are ceftriaxone, rifampicin and ciprofloxacin. Rifampicin is usually the drug of choice, but in view of emergence of resistant isolates, they recommend caution in its use during outbreaks. They recommend considering use of ciprofloxacin and ceftriaxone as there have been no development of resistance to them. Ciprofloxacin can be given in a single dose thus ensuring compliance and minimal side-effects, but is contraindicated in pregnancy and children. Ceftriaxone is safe for children and pregnant woman. It is administered in a single intramuscular dose to ensure adherence to prophylaxis, even though it causes more frequent but mild adverse effects compared with rifampicin.

Cochrane review of antibiotic prophylaxis for preventing meningitis with basilar skull fractures

Basilar skull fractures (BSF) may place the central nervous system in direct contact with bacteria from paranasal sinuses, nasopharynx or middle ear. Association of cerebrospinal fluid (CSF) leak with the fractures indicates torn duramater and increases risk of developing meningitis.[20] The main objective of this review was to determine whether prophylactic antibiotics administered as soon as a diagnosis of BSF is made (with or without CSF leakage), decreases the incidence of meningitis compared with no antibiotic.

The last search of the literature for this Cochrane review was carried out in September 2005. The authors included both randomized and non-randomized controlled trials, comparing any antibiotic with placebo or no intervention. Patients of all ages, with or without CSF leakage, were included. Frequency of meningitis, mortality and non-CNS infection were the outcome measures.

Four RCTs with 208 patients were included in the meta-analysis in general. The quality of the trials was poor. No statistically significant differences were found in the frequency of meningitis (Peto odds ratio [OR] 0.68; 95% CI or 0.28–1.65), mortality (Peto OR 1.76; 95% CI 0.41–7.60) or non-CNS infection (Peto OR 0.62; 95% CI 0.16–2.41). No statistically significant differences were found in the subgroups of patients with or without CSF leakage (Peto OR 0.37; 95% CI 0.06–2.24 vs. Peto OR 0.77; 95% CI 0.25–2.38, respectively). Meta-analysis of 17 non-RCTs with 2168 patients (treatment group 1141; control group 1027) yielded similar results (OR 1.13; 95% CI 0.67–1.88). However, all the above 95% CIs are very wide and do not exclude a clinically important difference.

The authors concluded that there is insufficient evidence to support or refute the use of antibiotics in the prophylaxis of meningitis in patients with BSF. Large, methodologically sound studies are needed.

Discussion

ABM is associated with high mortality and morbidity.[21] Prevention strategies can minimize mortality and morbidity. We found five Cochrane reviews that focused on prevention of ABM. The preventive strategies reviewed were vaccines (three reviews) and antibiotics (two reviews).

In reviews on prevention, the most recent search was carried out between 2004 and 2006. They show that the available vaccines are immunogenic and safe. There is evidence to show that polysaccharide serogroup A vaccine protects against serogroup A meningococcal disease. Conjugate vaccines against subgroup C meningococcal disease generate higher levels of titers of protective antibodies than the polysaccharide vaccines. Chemoprophylaxis is effective in eradicating carrier sate. These reviews raise a very important question. When dealing with a life-threatening disease such as meningitis, should or should we not accept evidence on surrogate outcomes (such as antibody titers or carrier eradication rate) as sufficient to make recommendations. This issue has been discussed in detail by Bucher et al.[22] If surrogate outcomes are strongly correlated with the final outcomes, and if multiple studies consistently show benefit in term of the surrogate outcomes, then it may be acceptable to recommend the intervention. Therefore, it seems that further clinical trials to demonstrate clinical effectiveness to conjugate meningococcal subgroup C vaccines may be unnecessary and probably unethical. However, lack of lasting immunity of polysaccharide meningococcal A vaccine and its uncertain efficacy in infants calls for urgent development and clinical testing of conjugate vaccines that are undergoing immunogenicity trials.[23] The availability of effective vaccine may not be enough to control (or hopefully eradicate in due course) the meningococcal disease. What is required is a policy and effective implementation of the policy by vaccinating people on a scale that will prevent the disease from occurring.

In this context, a noteworthy point is that childhood Hib meningitis has nearly been eliminated in the Western world after routine vaccination with conjugate Hib vaccines.[24] Some countries may consider introducing the vaccines to prevent meningococcal disease in their national

immunization programs, depending on public health burden and cost-effectiveness.

Others may consider selective immunization to high-side groups. In high-risk people, antibiotic prophylaxis is also an effective strategy to prevent or eradicate carriage. However, most antibiotic studies provided evidence of efficacy during the first 1 or 2 weeks. Only rifampicin has been studied up to 4 weeks.[24] Role of antibiotics in preventing meningitis after BSF remains unclear.

The vaccine reviews need to be updated as and when new trials are published, although it is probably unethical to conduct placebo-controlled trials of a new vaccine. Certainly, attempts to develop conjugate meningococcal serogroup A vaccines are on the horizon.[25,26] No Cochrane review on meningococcal serogroup B vaccine has been conducted. Such a review is important because serogroup B meningococcus accounts for 68% of cases reported in Europe from 1993 to 1996, and has also caused outbreaks in developed countries with attack rates of 5–50 cases per 100,000 persons.[27] Meningitis in countries such as New Zealand has increased because of meningococcal serogroup B.[28]

The Cochrane reviews presented here provide methodologically sound evidence because all have focused on RCTs. However, some[3] have included observational studies. The extent of bias in these studies is unclear, but similarity of the effect estimates provides assurance that the bias is unlikely to be higher.

Conclusions

Cochrane systematic reviews support the use of polysaccharide serogroup A vaccine to prevent serogroup A meningococcal meningitis, MCC vaccines to prevent meningococcal C meningitis and Hib conjugate vaccine to prevent Hib infections. There is a lack of evidence for or against the use of prophylactic antibiotics to prevent meningitis in patients with BSF. More studies are required to compare the relative effectiveness of ceftriaxone, ciprofloxacin and rifampicin in chemoprophylaxis against meningococcal infection.

Practice points

- Polysaccharide serogroup A vaccine is effective in preventing serogroup A meningococcal meningitis in adults as well as children beyond 3 months of age.
- MCC vaccine is effective in preventing meningococcal C meningitis and may be included in the National Immunology Program in areas where meningococcal disease is a substantial public health problem.
- Use of Hib conjugate vaccine is safe and effective for Hib-invasive disease.
- Ciprofloxacin may be the antibiotic of choice for chemoprophylaxis against meningococcal meningitis except in children and pregnant women for whom ceftriaxone may be the drug of choice.
- Insufficient evidence exists for or against the use of antibiotics to prevent meningitis in patients with BSF.

Research directions

- Correlation between antibody levels induced by polysaccharide serogroup A vaccine and clinical protection needs to be studied through systematic reviews and observational studies.
- More studies of MCC vaccines are required to address the immunogenicity of MCC at different time schedules and to analyze the influence of other vaccines given concomitantly. There is a need for a Cochrane review on meningococcal serogroup B vaccine.
- Vaccine field trials are required to evaluate the effects of Hib conjugate vaccine on either Hib-specific or on all-cause mortality.
- Trials comparing the relative effectiveness of ceftriaxone, ciprofloxacin, rifampicin and oral third-generation cephalosporins for eradication of *N. meningitidis* are needed.
- Large methodologically sound studies are needed to evaluate the effectiveness of prophylactic antibiotics in case of patients with BSFs.

Conflict of interest statement

I hereby confirm that none of the authors have a conflict of interest to declare in relation to this work.

References

1. Van de Beek D, Schmand B, De Gans J, et al. Cognitive impairment in adults with good recovery after bacterial meningitis. *J Infect Dis* 2002;**186**:1047–52.
2. Patel M, Lee CK, Polysaccharide vaccines for preventing serogroup A meningococcal meningitis; *Cochrane Database of Systematic Reviews* 2005; (1).
3. Conterno LO, Silva Filho CR, Ruggeberg JU, Heath PT. Conjugate vaccines for preventing meningococcal C meningitis and septicaemia. *Cochrane Database of Systematic Reviews* 2006; (3).
4. Swingler G, Fransman D, Hussey G. Conjugate vaccines for preventing *Haemophilus influenzae* type B infections. *Cochrane Database of Systematic Reviews* 2003; (4).
5. Fraser A, Gafter-Gvill A, Paul M, Leibovici L. Antibiotics for preventing meningococcal infections. *Cochrane Database of Systematic Reviews* 2005; (1).
6. Ratilal B, Costa J, Sampaio C. Antibiotic prophylaxis for preventing meningitis in patients with basilar skull fractures. *Cochrane Database of Systematic Reviews* 2006; (1).
7. Maiden MJC, Caugant DA. The population biology of *Neisseria meningitidis*: implications for meningococcal disease, epidemiology and control. In: Frosch M, Maiden MCJ, editors. *Handbook of meningococcal disease: infection biology, vaccination, clinical management*. Chichester: Wiley-VCH; 2006.
8. van Deuren, Brandtzaeg P, van der Meer JWM. Update on meningococcal disease with emphasis on pathogenesis and clinical management. *Clin Microbiol Rev* 2000;**13**:144–66.
9. IFRC, MSF, UNICEF, WHO Appeal for Meningococcal Meningitis Control in Countries at Risk in the African Continent, 1997–2000. Global Meningococcal Disease Update: www.who.int/emc/diseases/meningitisor, www.who.int/vaccines-diseases/meningitis_distr.htm. 1997 (last accessed 12 June 2007).
10. Ebrahim GJ. Meningococcal meningitis. *J Trop Pediatr* 1997; **43**:126–7.

11. Snape M, Pollard A. Meningococcal polysaccharide–protein conjugate vaccines. *Lancet Infect Dis* 2005;**5**:21–30.
12. Goldschneider I, Gotschliche EC, Malcolm S. Artenstein. Human immunity to the meningococcus. The role of humoral antibodies. *J Exp Med* 1969;**129**:1307–26.
13. Suker J, Feavers IM. Prospects offered by genome studies for combating meningococcal disease by vaccination. *Fut Med* 2001;**2**:273–83.
14. White M. Heath preventative strategies on meningococcal disease. *Arch Dis Child* 1997;**76**:178–81.
15. Gold R, Lenow ML, Goldschneider I, Draper TL, Gotschich EC. Clinical evaluation of group A and group C meningococcal polysaccharide vaccines in infants. *J Clin Invest* 1975;**56**:1536–47.
16. Taunay AE, Galvao JS, de Morais EC, Gotschlich EC. Disease prevention by meningococcal serogroup C polysaccharide vaccine in pre-school children: results after eleven months in Sao Paulo, Brazil abstract. *Pediatr Res* 1974;**8**:429.
17. Farrington C P. Estimation of vaccine effectiveness using the screening method. *Int J Epidemiol* 1993;**22**:742–6.
18. Hatton P. The use of the screening technique as a method of rapidly estimating vaccine efficacy. *Publ Health* 1990;**104**:21–5.
19. Pollard AJ. Meningococcal disease and healthcare workers: the risks to healthcare workers are very low. *BMJ* 1999;**319**:1147–8.
20. Katzen JT, Jarrahy R, Eby JB, Mathiasen RA, Margulies DR, Shahinian HK. Craniofacial and skull base trauma. Available at: www.skullbaseinstitute.com (last accessed 12 June 2007).
21. Daoud AS, Al-Sheyyab M, Batchoun RG, Rawashdeh MO, Nussair MM, Pugh RNH. Bacterial meningitis: still a cause of high mortality and severe neurological morbidity in childhood. *J Trop Pediatr* 1995;**41**:308–10.
22. Bucher HC, Kunz R, Cook D, Holbrook A, Guyatt G. Therapy and applying the results of surrogate outcomes. In: Guyatt G, Rennie D, editors. *Users' guides to the medical literature: a manual for evidence-based clinical practice*. Chicago: American Medical Association; 2002.
23. Joseph H, Ryall R, Bybel M, et al. Immunogenecity and immunological priming of serogroup a portion of a bivalent meningococcal A/C conjugate vaccine in 2 year old children. *J Infect Dis* 2003;**1**:1142–6.
24. Schuchat A, robinson K, Wenger JD, Harrison LH, Farley M, Reingold AL. Bacterial meningitis in the United States in 1995: active surveillience team. *N Engl J Med* 1997;**337**:970–6.
25. W.H.O. State of the world's vaccines and immunization, revised edn. World Health Organization; 2003.
26. Anonymous. The evolving vaccine pipeline; www.who.int/entity/immunization_delivery/new_vaccines/Evolving-vaccine-pipeline.pdf (last accessed 12 June 2007).
27. Rosenstein NE, Perkins BA, Stephens DS, Popovic T, Hughes JM. Meningococcal disease. *N Engl J Med* 2001;**344**:1378–88.
28. Sáfadi MAP, Barros AP. Meningococcal conjugate vaccines: efficacy and new combinations. *J Pediatr (Rio J)* 2006;**82**: S35–44.